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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/612,104	07/02/2003	Adam Wieslaw Mazur	7490MC	3400

27752 7590 02/01/2005

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 02/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/612,104	MAZUR ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *3 and 5-8* is/are allowed.

6)☒ Claim(s) *1,9 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

This application contains at least one sequence disclosure that is encompassed by the definitions for amino acid sequences set forth in 37 CFR 1.821. However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 with regard to the sequence disclosures.

See, for example, the sequence on page 14, line 13 (Tyr-Phe-Arg-Trp).

Applicant is given the time period set in this letter within which to comply with the sequence rules, 37 CFR 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136. In no case may an applicant extend the period for response beyond the six month statutory period.

✧

The specification is objected to. On pages 32-35 several figures are shown. 37 CFR 1.58 authorizes an examiner to require formal drawings in lieu of graphs that are inserted into the specification. While it is noted that exceptions are made on occasion, the fact is that the graphs on pages 32-35 are critical to the practice and understanding of the invention, and are critical to all enablement issues. In addition to the criticality of these graphs, there are two other issues. First, in several of these (e.g., the first two on page 32), the data points of "3R" are not clear. These data points must be clear not only to the examiner, but to persons responsible for printing the final document. In addition, the "X-axis" is not labelled; presumably it should recite concentration. In a related vein, the numbers on the "X-axis" are rather cryptic. Presumably, the three data points should read 1×10^{-8}, 1×10^{-6}, and 1×10^{-4}, respectively. This is not clear from the graphs. Also, on the second graph on page 33, the designation "2 exp" appears.

Submission of formal drawings is required, accompanied by deletion of the graphs from pages 32-35. The formal drawings must conform to 37 CFR 1.81. In addition, figure legends are required.

✧

Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 10 of U.S. Patent No. 6613874. Although the conflicting claims are not identical, they are not patentably distinct from each other. There is overlap of the claimed genera.

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. In re Vogel, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application . See 37 CFR 1.78(d)

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-10 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have provided graphs (pp. 32-35) which presumably convey some kind of *in vitro* activity. However, the term "1R", "3R" and "4R" are not identified, so it is not possible to tell what was done or what the graphs mean. However, it does seem possible that one or more of the peptides have some effect on cAMP activity when certain conditions are met. What those conditions might

be have not been identified. It is unclear what experiments were actually carried out. There is a brief mention of an experimental objective on page 11, line 1+, and page 31, and this may (or may not) have something to do with what is disclosed in Chen (*Analytical Biochemistry* 226 (2) 349-54, 1995).

In addition to the foregoing, on page 55 of the specification, an experiment is described in which it is asserted that the patient exhibits "measurable weight loss". The present tense is used, rather than the past tense. Accordingly, this is regarded as a proposal for a future experiment, rather than an actual result. But even if the patient did indeed exhibit "measurable weight loss", this is not especially meaningful. First, there is the matter of experimental controls. That is, one person might be administered a compound according to claim 1 and "lose" 1/2 a pound; a second person might be give a placebo and lose 2 pounds. Which is more effective, the compound of claim 1 or the placebo? Moreover, even with controls, the results have no meaning, in part because the term "weight loss" could refer to just a day to day fluctuation, or even a fluctuation that occurs over a period of about 10 hours. Over the course of 24 hours, the weight of the typical adult wil certainly vary by at least 100 grams. An adult might weigh 150.2 pounds at 11 P.M. on a given night, and weigh only 150 pounds at 11:00 the next morning. Thus, to say that a person's weight has decreased is not particularly informative. In addition to the foregoing, there is the matter of incentives. A person who is offered an incentive is going to be more likely to

lose weight than another person without the incentive. As for extrapolation from the in vitro experiments to a conclusion of attainment of weight loss, there is unpredictability with respect to this. Proposals and experiments for treatment of obesity have been reviewed in Kordik (*J. Med. Chem.* 42, 181-201, 1999). As is evident, there have been some limited successes. But the failures outnumber the successes; in any case, there is ample evidence presented in the article to support an assertion of unpredictability.

It may turn out that there is enablement for the following claim:

> *100. A method of stimulating the MC-4 (melanocortin-4) receptor in a mammal comprising administering to a mammal in need thereof a cyclic peptide according to claim 1 for a time and under conditions effective to stimulate the MC-4 receptor.*

It may also to turn out to be the case that the following claim is enabled (though not necessarily described in the specification):

> *101 . A method of suppressing appetite in a human who is endeavoring to reduce caloric intake comprising administering to said human a cyclic peptide of claim 1 for a time and under conditions effective to stimulate the MC-4 receptor.*

One issue is whether the degree of stimulation of the MC-4 receptor is sufficient to achieve benefit. A second issue is, even if the the cells bearing MC-4 receptors are stimulated to their ultimate capacity to generate cAMP, will there necessarily be a perceptible effect on the course of the disease in question? Is

there any indication that any of the recited diseases is so critically dependent on MC-4 that stimulation or antagonism of this receptor will result in a perceptible effect? There is no evidence that this is the case.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. Applicants' assertions are founded on experimental results which are only barely described, and which tend to indicate that if cells bearing MC-3 or MC-4 receptors are brought into contact with a peptide encompassed by claim 1, that some cAMP will be produced. However, what this might mean for the various "downstream" events which are mediated by the MC-4 receptor is not clear. Xiao (*Biochemistry* 40, 2860, 2001) has looked at the relationship between cAMP production in cells, and in vivo activity. While some degree of correlation was noted, a 1:1 correspondence was absent. This absence of 1:1 correspondence is sufficient to support an assertion of "unpredictability".

Consider the following:

- Torsello, Antonio (*Endocrinology* 143 (5) 1968, 2002) pertains to growth hormone, and discloses that stimulation of the growth hormone secretagogue receptor does not correlate with capability to stimulate GH secretion.

- McFadyen "Modifications of the cyclic mu receptor selective tetrapeptide Tyr-c[D-Cys-Phe-D-Pen]NH(Et): effects on opioid receptor binding and activation" (*Journal of Peptide Research* (2000 Mar) 55 (3) 255-61) reported on modifications to the title peptide. The reference discloses that potency changes did not always correlate with affinity, suggesting that the conformation required for binding and the conformation required for activation of the opioid receptors are different.

- Keith , "mu-Opioid receptor internalization: opiate drugs have differential effects on a conserved endocytic mechanism in vitro and in the mammalian brain" (*Molecular Pharmacology* 53 (3) 377-84, 1998) discloses that the different effects of individual agonists are not correlated with their potencies for receptor activation and that a variety of clinically important agonists differ significantly in their relative abilities to stimulate the rapid internalization of opioid receptors.

- Xiao (*Biochemistry* 40, 2860, 2001) has looked at the relationship between cAMP production in cells, and in vivo activity. While some degree of correlation was noted, a 1:1 correspondence was absent. As stated on page 2864, col 2, "the results indicated that these functions may be dissociated, mostly likely to additional determinantants of in vivo activity...". For example, as conveyed in table 6, Phe'-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 along with decreased in vivo insulinotropic activity; by contrast, Acetyl-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 accompanied by an increase in in vivo insulinotropic activity. Thus, receptor activation is not necessarily predictive of in vivo activity.

- Lunec, "MSH receptor expression and the relationship to melanogenesis and metastatic activity in B16 melanoma" (*Melanoma Research* (1992 May) **2** (1) 5-12) compared the effects of different pro-opiomelanocortin (POMC) peptides on melanogenesis and metastasis and their relationship to MSH receptor expression in B16F1 melanoma cells. The authors disclose that the relative binding affinities of the different peptides, measured by displacement of [^{125}I]-Nle^{4}-D-Phe^{7}-alpha-MSH, did not closely correlate with the relative potencies in stimulating melanogenesis and metastasis. This suggests that receptor activation and the subsequent biological response is not determined solely by binding affinity.

In accordance with the foregoing, it is clear that whether one is endeavoring to stimulate a receptor in vitro or to antagonize a receptor *in vitro*, extrapolating to a therapeutic method leads to "unpredictable" results. Moreover, as indicated above, attempts to treat obesity based on results of in vitro experiments leads to "unpredictable" results, as disclosed in Kordik (*J. Med. Chem.* 42, 181-201, 1999). In addition to those examples of "failure", Bray (*Endocrine Reviews* 20, 805-875, 1999) provides more examples of "failure" in the treatment of obesity.

In accordance with the foregoing, extrapolation from stimulation of cAMP production in a petri dish to treatment of obesity will produce an "unpredictable" outcome. Accordingly, "undue experimentation" would be required to practice the claimed invention.

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Claims 9-10 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9-10 are indefinite as to the endpoint of the treatment. A related issue concerns the question of whether the peptide is to be administered to a mammal who is not obese or who would not derive benefit from it. For example, would the peptides be administered to an anorexic human, or to a polar bear at the onset of winter?

✧

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached at 571-272-0925. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.